Drugs that act on the respiratory tract

Dinesh Yogaratnam, PharmD, BCPS, BCCCP*,
Katherine M. Carey, PharmD, BCACP, Valerie Coppenrath, PharmD,
Aimee Dawson, PharmD, Morgan Harris, PharmD,
Amy B.W. LaMothe, PharmD, BCPS, Pourya Pourhosseini, PharmD,
and Ann M. Lynch, BSP, PharmD, AE-C

MCPHS University, School of Pharmacy-Worcester/Manchester, Worcester, MA, United States
*Corresponding author: dinesh.yogaratnam@mcphs.edu

LEUKOTRIENE MODIFIERS [SEDA-36, 245; SEDA-37, 197; SEDA-38, 160; SEDA-39, 166; SEDA-40, 219; SEDA-41, 172; SEDA-42, 172]

The leukotriene-modifying agents (LTMA) include the leukotriene receptor antagonists (LTRA) montelukast, zafirlukast, and pranlukast, as well as the leukotriene synthesis inhibitor, zileuton. Pranlukast is not available in the United States, but it is used widely in some other countries. In 2020, a US Food and Drug Administration (FDA) labeling change and one study with clinical relevance to adverse effects of montelukast were published. No studies were identified for the other leukotriene-modifying agents.

In March of 2020, the FDA announced that the product labeling for montelukast would change to include a Boxed Warning about serious neuropsychiatric events (NEs), including depression, anxiety, sleep disturbances, and suicide (US Food and Drug Administration, 2020 [S]). This decision was based upon the FDA's reevaluation of the risks and benefits of montelukast. A review of the FDA Adverse Event Reporting System (FAERS) database from the drug's approval in February 1998 through May 2019 identified 82 cases of completed suicide associated with montelukast; 45 cases were in adult patients and 19 were in pediatric patients younger than 18 years (18 cases did not provide the age of the patient). Using data from the FDA's Sentinel System, an observational study of 457 377 patients examined if the risk of serious NE differed between montelukast and inhaled corticosteroids for patients with asthma (Sentinel Initiative (2019) [C]). This study found no significant differences in the risk of inpatient depressive disorder (hazard ratio [HR] 1.06; 95% confidence intervals [CI] 0.90–1.24) or self-harm (HR 0.92; 95% CI 0.69–1.21). There were 4 reported suicides, 2 in each study group. While the FDA's internal study did not show significant increases in the risk of certain NEs, a panel of outside experts made the recommendation to the FDA to strengthen the warnings of montelukast's product labeling out of an abundance of caution (US Food and Drug Administration, 2020 [S]). The FDA now recommends that montelukast be reserved for patients with allergic rhinitis who fail other available therapies and be considered for patients with asthma in whom the benefit is expected to outweigh the risk of serious NEs.

Di Salvo and coauthors conducted a review of the literature to examine the incidence of adverse skin reactions associated with use of montelukast (Di Salvo et al., 2020 [A]). The review identified 17 case reports published between 2000 and 2014. A total of 8 probable or potential cases of montelukast-induced eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, were published. This adverse effect is a rare, necrotizing vasculitis of small- and medium-sized vessels associated with eosinophilia. Cases included 5 women and 3 men (aged 37–68 years) who had been taking montelukast for between 1 month and 1 year prior to EGPA onset. Most of the cases reported that following discontinuation of montelukast, symptoms resolved, although some cases did not report whether or not there was resolution after discontinuation. Additional cases of rash, vesicles, or painful, cutaneous lesions were reported in 2 women and 2 men. A case series reported a patient

who developed progressive numbness and pain in the arms and legs, as well as another patient who developed malaise, myalgia, and purpura in both legs. The authors also identified 5 cases of urticaria with or without angioedema. Patients ranged in age from 23 to 50 years and were both male and female. The cases of urticaria or angioedema appeared between 1 dose and 1 month after taking the montelukast, and reappeared within days of rechallenge, which, the authors postulated, suggested a sensitization period and, thus, an immunological mechanism.

ANTICHOLINERGIC DRUGS [SEDA-36, 245; SEDA-37, 197; SEDA-38, 158; SEDA-39, 165; SEDA-40, 222; SEDA-41, 175; SEDA-42, 173]

Inhaled anticholinergic drugs continue to play a prominent role in managing chronic obstructive pulmonary disease (COPD) and an increasingly important role in the treatment of persistent asthma. In general, these agents are well-tolerated, with xerostomia being the most common adverse effect. The cardiovascular safety of long-acting muscarinic antagonists (LAMAs) were recently evaluated in two large meta analyses (Lee et al., 2020 [M]; Yang, Zhang, et al., 2020 [M]). A case report describes an ocular side-effect associated with nebulized ipratropium therapy (Banerjee et al., 2020 [A]). The safety of tiotropium in pediatric patients was also recently evaluated in both a systemic review and a meta-analysis (Sunther et al., 2021 [M]; Yang, Peng, et al., 2020 [M]). Lastly, the safety of umeclidinium, as part of a combination inhaler, was evaluated in a large randomized clinical trial (Lee et al., 2021 [C]).

A large systematic review and Bayesian network meta-analysis that included 16 randomized controlled trials (RCTs) of patients with stable COPD treated with long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs) combinations was published in 2020 (Lee et al., 2020 [M]). The LAMAs included in this meta-analysis were aclidinium, glycopyrrolate, tiotropium with a dry powder inhaler or soft mist inhaler, and umeclidinium. One of the study outcomes was the rate of major adverse cardiovascular events (MACE), and nine of the RCTs reported data on this metric. There were no significant differences in the risk of MACE found between any of the LAMA/LABA combinations. Another large meta-analysis that included 20 RCTs investigated MACE with tiotropium also concluded that tiotropium was not associated with an increased risk of MACE regardless of the duration of treatment (Yang, Zhang, et al., 2020 [M]).

Ipratropium

A case report from the United Kingdom describes nebulized ipratropium bromide associated with the development of mydriasis of the left eye of a young boy (Banerjee et al., 2020 [A]). A 3-year-old boy presented with anisocoria (unequal pupils) following treatment of acute respiratory distress with nebulized ipratropium. This caused concern for the clinicians and parents as the patient has a complex medical history including a ventriculoperitoneal (VP) shunt on left side from an obstructive hydrocephalus secondary to grade 4 intraventricular hemorrhage. This anisocoria could have been a symptom of VP shunt blockage, which if not addressed urgently could result in serious complications including death. Fortunately, clinicians identified the anisocoria was a result of the nebulized ipratropium bromide being administered via an improperly fitted facemask. This caused enough drug to come in contact with the patient's left eye, resulting in acute pupil dilation due to ipratropium's anticholinergic properties. The adverse event resolved within 24 h of discontinuation of the nebulized ipratropium. This case report underscores the importance of proper administration of nebulized solutions to minimize potential adverse events.

Tiotropium

Tiotropium is increasingly being investigated for its role in treatment of pediatric and adolescent asthma. One meta-analysis and one systematic review have been published this year investigating the safety and efficacy of this agent within this population (Yang, Peng, et al., 2020 [M]; (Sunther et al., 2021) [M]). Both articles included 7 studies each investigating tiotropium for the management of asthma in children aged 6–17 years old. The systematic review elected to include an article that did not meet the inclusion criteria as it included young patients aged 1–5 years (Sunther et al., 2021 [M]). Both the systematic review and meta-analysis concluded that tiotropium is safe and well tolerated in children with asthma. Adverse events were deemed to occur at similar rates as placebo and were mild to moderate in nature. Common adverse events included nasopharyngitis, asthma, bronchitis, and pharyngitis. Of note, the meta-analysis found that tiotropium significantly increased the rate of headache in this pediatric population (RR, 3.93; 95% CI, 1.20–12.90; $P = 0.02$) (Yang, Peng, et al., 2020 [M]).

Umeclidinium

The CAPTAIN trial was a double-blind, randomized, phase 3A trial investigating the efficacy and safety of once daily single inhaler triple therapy fluticasone furoate plus umeclidinium plus vilanterol (FF/UMEC/VI) compared

with FF/VI (Lee et al., 2020 [C]). Adverse events were mild and typical, with nasopharyngitis occurring 13–15% and headache occurring 5–9%. Both the overall adverse event and serious event rates were expected and equal between both groups. Notably, three deaths occurred in the trial with one death deemed to be related to the study drug, FF/UMEC/VI 100/31·25/25 μg. This patient experienced a pulmonary embolism. The authors do not provide additional information related to this mortality event. Overall, this study provides evidence that umeclidinium is generally safe to use as part of a triple-drug inhaler product.

ANTI-FIBROTIC THERAPIES [SEDA-40, 224; SEDA-41, 177; SEDA-42, 175]

Nintedanib and pirfenidone are oral anti-fibrotic drugs used to slow the progression of idiopathic pulmonary fibrosis (IPF). A number of recent "real-world", observational, and retrospective studies (Antoniou et al., 2020 [C]; Cameli et al., 2020 [C]; Chung et al., 2020 [C]; Corral et al., 2020 [C]; Dhooria et al., 2020 [C]; Eaden et al., 2020 [C]; Harari et al., 2020 [c]; Justet et al., 2021 [c]; Lasky et al., 2020 [C]; Majewski et al., 2020 [C]; Senoo et al., 2020 [c]; Takeda et al., 2020 [c]; Uchida et al., 2021 [c]; Vianello et al., 2020 [c]), an open-label extension study (Song et al., 2020 [C]), a small, prospective, patient-satisfaction study (Moor et al., 2020 [c], and a post-hoc analysis (Richeldi et al., 2020 [C]) further describe the safety profile of these drugs among patients with IPF from different nations, with more advanced disease, with advanced age, or who have been switched from nintedanib to pirfenidone. In these studies, the type, frequency, and severity of adverse drug events were similar to previously published clinical trial results and showed no new signals of adverse drug events with either nintedanib or pirfenidone. Some of these reports suggest that advanced age, low body mass index, and low % forced vital capacity may be independent risk factors for drug-related adverse events, including early drug discontinuation (Dhooria et al., 2020 [C]; Uchida et al., 2021 [c]). However, these findings have not been consistently observed in other trials; these potential risk factors need to be validated with data that are more robust. In addition, there is continued interest in evaluating nintedanib and pirfenidone for illnesses other than IPF. Pirfenidone has been studied as a perioperative therapy in patients undergoing surgical resection of primary lung cancer (Kanayama et al., 2020 [c]), as well as a maintenance therapy in patients with unclassifiable progressive fibrosing interstitial lung disease (Maher et al., 2020 [C]) and systemic sclerosis-related interstitial lung disease (Acharya et al., 2020 [c]). Nintedanib use has been reported in progressive interstitial lung disease

(Wells et al., 2020 [C]), non-small cell lung cancer with IPF (Shiratori et al., 2020 [A]), idiopathic-inflammatory-myopathy-related interstitial lung disease (Liang et al., 2021 [c]), rheumatoid arthritis-related interstitial lung disease (Narváez et al., 2020 [A]; Vacchi et al., 2020 [A]), systemic sclerosis-related interstitial lung disease (Azuma et al., 2021 [C]; Bournia et al., 2021 [R]; Highland et al., 2021 [C]; Kuwana et al., 2021 [c]; Seibold et al., 2020 [C]), bronchiolitis obliterans syndrome after allogenic haematopoietic stem cell transplantation (Tang et al., 2020 [A]), and for pulmonary fibrosis after coronavirus disease 2019 (Ogata et al., 2021 [A]). The incidence, type, and severity of nintendanib and pirfenidone associated adverse events in these reports is consistent with what has been previously reported for these agents in clinical trials for IPF. While a literature review from Bournia et al. (2021) [R] suggests that incidence of nintedanib-induced diarrhea among patients with systemic sclerosis-associated interstitial lung disease may be influenced by a nocebo effect in this particular patient population, this hypothesis requires further study in order to be validated. Described in more detail below, there are 5 case reports for nintedanib and 2 case reports for pirfenidone describing rare adverse reactions for these agents (Amini et al., 2020 [A]; Arunprasath et al., 2020 [A]; Dull et al., 2020 [A]; Hasegawa et al., 2020 [A]; Imai & Tomishima, 2020 [A]; Jiménez et al., 2020 [A]; Madgula et al., 2020 [A]).

Nintedanib case reports

A case report from the United States describes a 68-year-old man who experienced nintedanib-induced colitis that was effectively treated with oral budesonide (Amini et al., 2020 [A]). The patient had been taking nintedanib 150 mg twice daily for IPF for 3 years. During this time, he developed diarrhea, a known and common side effect of nintedanib. He had been managing his diarrhea with twice-daily cholestyramine, but his diarrhea acutely worsened, which prompted further evaluation. The patient's vital signs and laboratory work up were unremarkable with the exception of a mildly elevated C-reactive protein level (the exact value is not reported). He reported no abdominal pain and no nausea. A colonoscopy revealed "…diffuse areas of erythematous, friable, and granular mucosa throughout the entire colon…" A biopsy of the colon revealed a histological pattern consistent with acute inflammation and "expansion of the lamina propria by lymphoplasmacytic infiltrate." The patient's colitis was presumed to be due to the nintedanib, but a Naranjo score is not provided. While diarrhea is a common adverse event associated with nintedanib, colitis has been rarely reported (Chandler, 2020 [R]). The mechanism for this adverse drug reaction remains unknown but

could possibly be associated with nintedanib metabolites that are excreted into the intestines or reduced intestinal perfusion due to nintedanib's inhibition of vascular endothelial growth factor (VEGF). What is noteworthy about this case is that the patient continued to receive his nintedanib at full dose. To manage his colitis, he was started on 9 mg budesonide (frequency not stated), and his colitis completely resolved 4 months later. The authors mention that they had planned to titrate the budesonide to the lowest possible dose, but they do not state whether or how the budesonide continued after the 4-month follow up appointment. To manage nintedanib-induced diarrhea, other authors have suggested either reducing the dose of nintedanib or using multiple anti-diarrhea medications (Hirasawa et al., 2020 [c]). It does not appear that either of these strategies were employed in this case. The decision to use systemic corticosteroids to treat nintedanib-associated colitis requires careful consideration of the risks and benefits vs these alternative strategies.

A case report from Japan describes a 68-year-old man with IPF who developed glomerular microangiopathy (GMA) soon after initiation of nintedanib (Hasegawa et al., 2020 [A]). The patient was a heavy smoker, who reportedly smoked 50 cigarettes per day for 48 years. In addition to IPF, his past medical history included pleomorphic carcinoma of the lung, for which he had undergone a partial lung resection, and primary aldosteronism. His home medications included nintedanib 300 mg per day, eplerenon 100 mg per day, and amlodipine 2.5 mg per day. Four months prior to presentation, the patient had a normal serum creatinine and no evidence of either hematuria or proteinuria. One week after starting nintedanib 300 mg per day, the patient developed proteinuria 2+ and hematuria 1+, symptoms of diarrhea and nausea, and an increase in blood pressure. Ten months after nintedanib initiation, the patient was developed worsening proteinuria and leg edema, so he underwent a kidney biopsy for further evaluation. The biopsy revealed patchy tubular atrophy and interstitial enlargement. The glomeruli showed "mild mesangial proliferation and widely expanded subendothelial area occupied by hyaline-like materials with some huge subendothelial deposition." The histologic examination was consistent with a diagnosis of glomerular microangiopathy. The nintedanib was subsequently discontinued, and the patient was treated with furosemide 20 mg per day and trichlormethiazide 1 mg per day. The hematuria resolved within 1 month, and the proteinuria improved over the course of 3 months. The authors report that over the next 2 years of follow-up monitoring, the patient's GMA did not return. A Naranjo score is not provided. This report is the second to describe nintedanib GMA. The mechanism for this reaction is unknown, but the authors hypothesize that nintedanib's ability to inhibit platelet-derived growth factor (PDGF) may impair the kidney's ability to repair itself when glomerular damage occurs. Clinicians should consider the possibility of nintedanib associated GMA in patients who develop unexplained proteinuria or hematuria.

A case report from Japan describes an 85-year-old man who developed left ventricular (LV) dysfunction shortly after starting nintedanib for treatment of IPF (Imai & Tomishima, 2020 [A]) The patient had a history of bladder cancer (in remission) hypertension, chronic kidney disease, and hypothyroidism. His blood pressure was noted to be well-controlled with medication therapy. His home medications included amlodipine, candesartan, and levothyroxine (doses not provided). The patient was a former smoker with a 27 pack-year history. The patient did not have any history of cardiac dysfunction. He started taking nintedanib 200 mg per day for newly diagnosed IPF, and this dose was increased to 300 mg per day. Two months after starting nintedanib, the patient presented to the hospital with a 3-day history of shortness of breath while at rest, orthopnea, and bilateral pitting edema of the lower extremeties. A transthoracic echocardiogram revealed a LV ejection fraction (LVEF) of 34%. Prior to starting nintedanib, his LVEF was 69%. A cardiac catheterization revealed no significant coronary stenosis. His laboratory workup revealed elevated N-terminal pro-brain natriuretic peptide (23 908 pg/mL) and a slightly elevated troponin T (0.063 ng/mL). Other than the newly started nintedanib, no other cause could be identified for why this patient had developed acute LV dysfunction. His nintedanib therapy was stopped, and he was started on heart-failure therapy with furosemide, nitroglycerine, candesartan, and carvedilol. By hospital day 8, the patient's LVEF had improved to 41%, and he was discharged from the hospital on day 18. His LVEF improved to 58% 3 months later during an outpatient evaluation, and the authors note that the patient has not had any signs of symptoms of heart failure since the initial acute episode. The authors assert that this is the first case of nintedanib-associated LV dysfunction. They attribute the patient's acute LV dysfunction to nintedanib since no other cause could be identified and the patient's condition improved soon after nintedanib discontinuation. A Narajno score is not provided. The authors note that nintedanib is a tyrosine kinase inhibitor (TKI), and that other TKIs have been shown to cause significant cardiovascular side effects, including LV dysfunction. Of note, other authors have also raised concern regarding nintedanib's cardiac safety, suggesting additional study and scrutiny may be required to better understand the cardiac risk profile of nintedanib (Ameri et al., 2021 [R]).

A case report from Spain describes an 88-year-old man who developed severe hepatotoxicity associated with nintedanib (Jiménez et al., 2020 [A]). The patient had been taking nintedanib for the past 2 years for IPF. The dose of nintedanib is not reported. However, it is noted

that the patient had a dose reduction "months ago" due to worsening of nintedanib-associated diarrhea. The patient presented with a 1-month history of weakness, weight loss, jaundice, and pruritus. He did not report abdominal pain. Laboratory tests revealed elevated bilirubin (total, direct, and indirect bilirubin levels were 3.7, 2.17, and 1.53 mg/dL, respectively), increased alkaline phosphatase (726 U/L), transaminitis (gamma-glutamyl transferase, glutamic oxaloacetic transaminase, and glutamate pyruvate transaminase were 904, 44, and 32 U/L, respectively), and a mild coagulopathy (INR 1.3). Of note, these laboratory abnormalities had been normal 8 months prior to presentation, and they began to worsen 4 months prior. A diagnostic workup did not identify a viral, other drug, toxin, neoplastic, or autoimmune cause of the patient's cholestatic liver damage. Nintedanib therapy was discontinued, and the patient was reported to have clinical and laboratory improvement by day 4. The patient continued to show improvement at his 4-month follow-up appointment. While the authors note that nintedanib has previously been associated with mixed liver injury, this is the first reported case of nintedanib-associated severe hepatotoxicity with jaundice. A Naranjo score is not provided, but this likely represents a possible association. Clinicians should monitor for signs and symptoms of liver dysfunction and consider nintedanib as a potential cause of hepatoxicity with jaundice.

A case from the United States describes a 72-year-old man who developed a systemic fungal infection, talaromycosis, while taking nintedanib for treatment of IPF (Madgula et al., 2020 [A]). The patient had been diagnosed with IPF 2 months prior to admission, and he was started on nintedanib therapy at that time (dose not provided). Of note, the patient tested negative for both tuberculosis and HIV. The patient presented to the hospital with dyspnea on exertion that had been getting progressively worse over the past 2 weeks. A CT scan of his chest revealed evidence of worsening interstitial lung disease, as well as a round soft-tissue density in the right upper lobe measuring 1.8 cm. This finding was compared to his previous CT scan, which showed the same lesion, but smaller at 1.3 cm. A biopsy was obtained via video assisted thoracoscopic surgery, and two fungal cultures from this procedure grew Talaromyces sp. The patient was started on vancomycin, cefepime, azithromycin, and liposomal amphotericin. The patient subsequently had his antifungal therapy switched to voriconazole because he had developed a hypersensitivity reaction amphotericin despite receiving premedication. The patient's respiratory condition worsened, he was placed on mechanical ventilation, his condition worsened, and he succumbed to multi-organ failure. The authors note that talaromycosis is a rare infection that is associated with immunocompromised conditions, such as acquired immunodeficiency syndrome

(AIDS); it is even more rarely seen in immunocompetent hosts. It remains unclear if either the patient's IPF or the nintedanib may have played a role in the development of talaromycosis in this patient. However, the authors suggest that there may be immune-modulating effects related to nintedanib's ability to inhibit tyrosine kinase that might increase one's risk of rare infections. A Naranjo score is not provided. Since the patient did not improve with withdrawal of nintedanib therapy, no previous reports of nintedanib-associated talaromycosis have been reported, and no definitive pathologic mechanism has been identified, the strength of association between nintedanib and talaromycosis remains weak.

Pirfenidone case reports

A report from India describes the case of a 70-year-old man who developed a phototoxic reaction while taking pirfenidone for treatment of newly diagnosed IPF (Arunprasath et al., 2020 [A]). The patient started taking pirfenidone 400 mg by mouth three times daily, then, after 2 months, the dose was increased to 600 mg three times daily. One month later, the patient developed "hyperpigmented itchy skin lesions involving the face, forearms, and thigs for 10 days." The damaged skin had clear, sharp margins that outlined sun-exposed areas. A histological examination also revealed epidermal necrosis and hyperkeratosis, as well as an inflammatory pattern consistent with a phototoxic drug reaction. Hematologic results from blood samples were within normal limits, and no other causes for the skin reaction could be identified. The patient was treated with steroids (dose, route and duration not specified) and sunscreens. The pirfenidone was also discontinued. The patient's skin lesions improved, but the degree to which they improved and the time course of improvement is not described. The authors conclude that pirfenidone was the probable culprit, with a Naranjo score of 6. The authors note that the patient's phototoxic reaction was not confirmed with a phototest. They also conclude that the patient's clinical presentation, histology, and laboratory work up were not consistent with photoallergy, a type of photosensitivity that has also been associated with pirfenidone. This report adds to our knowledge of pirfenidone-associated photosensitivity in that both allergic mechanisms (photoallergy) and non-allergic mechanisms (phototoxicity) can play a role in this adverse drug reaction. While patients with photoallergy should not be re-exposed to pirfenidone, it is not clear if patients with phototoxicity can be safely restarted on pirfenidone.

Three cases of diffuse alveolar hemorrhage (DAH) associated with pirfenidone therapy from the United States were recently reported (Dull et al., 2020 [A]).

All three patients had been taking pirfenidone 801 mg three times daily and were receiving home oxygen therapy for their IPF, and all three presented with shortness of breath and hemoptysis. The first case involved an 88-year-old woman, who was an active smoker, with a past medical history of COPD, stroke, hypertension, anxiety, arthritis, dementia, and depression. She started pirfenidone 7 weeks prior to admission. Her home medications also included albuterol, amlodipine, ascorbic acid, aspirin, atorvastatin, benzonatate, cholecalciferol, guaifenesin, nitroglycerin, omeprazole, prednisone, promethazine, and senna. She presented with a respiratory rate of 26 breaths per minute, heart rate of 108 beats per minute, blood pressure of 152/77 mm Hg, and an oxygen saturation of 79% on 4 L/min oxygen via nasal canula. A CT exam of her chest revealed findings consistent with alveolar hemorrhage, but this finding was not confirmed with a bronchoscopy. She was treated with ipratropium/albuterol, systemic corticosteroids, and antibiotics for possible COPD exacerbation, IPF exacerbation, and community acquired pneumonia. Her symptoms resolved, she was discharged from the hospital, and she was subsequently started on nintedanib maintenance therapy for her IPF. The second case involved a 75-year-old man who had stopped smoking 50 years ago, and who had a past medical history of hyperlipidemia, degenerative joint disease, GERD, stroke, hypertension, and obstructive sleep apnea. He started pirfenidone 4 months prior to admission. His home medications also included acetaminophen, aspirin, atorvastatin, escitalopram, gabapentin, glipizide, loratadine, losartan, metoprolol tartrate, multivitamin, omeprazole, and warfarin. Of note, his presenting INR was 1.7. This patient presented with a respiratory rate of 18 breaths per minute, a blood pressure of 90/55 mm Hg, and oxygen saturation of 90% on 4 L/min oxygen via nasal canula. A bronchoscopy revealed alveolar hemorrhage, and subsequent chest X-ray revealed evidence of possible inflammatory alveolitis. Despite treatment with intravenous steroids, the patient did not improve, so the patient's family decided to withdraw care and the patient expired on hospital day 5. The third case involved a 73-year-old man, who was an active smoker, who had a past medical history of uncomplicated type 2 diabetes mellitus, hypertension, and benign prostatic hypertrophy. He started pirfenidone 19 days prior to admission. His home medications also included glipizide, lisinopril, and multivitamin. He presented with a respiratory rate of 26 breaths per minute, heart rate of 91 beats per minute, blood pressure 101/59 mm Hg, and oxygen saturation of 88% on 4 L/min oxygen via nasal cannula. A bronchoscopy revealed evidence of DAH, and the patient was initiated on prednisone 60 mg daily. The patient recovered from this episode over the course of 10 days. These three cases were determined to have a possible association with pirfenidone; the Naranjo score was 3, 2, and 3 for the first, second, and third case, respectively. The authors note that an alternative explanation for the presence of DAH could have been due to these patients experiencing an acute exacerbation of IPF, which has been reported to be associated with diffuse alveolar damage, and, to a lesser extent, DAH. However, they further note that the radiographic evidence in these cases were not consistent with acute exacerbations of IPF. Thus, these reports are the first to identify DAH as a possible side effect of pirfenidone therapy, and clinicians should monitor their patients for the presence of blood in the sputum.

MONOCLONAL ANTIBODIES [SEDA-38, 161; SEDA-39, 167; SEDA-40, 225; SEDA-41, 179; SEDA-42, 178]

Currently, there are currently five monoclonal antibodies approved for the treatment of asthma: omalizumab, benralizumab, mepolizumab, reslizumab, and dupilumab. These agents inhibit various steps in eosinophil-mediated type-2 inflammation, which is present in up to 50% of patients with asthma. These agents are typically reserved for patients with moderate to severe asthma who have laboratory evidence of allergic or eosinophilic inflammation. Compared to typical asthma inhalers, these injectable agents are expensive and often require administration in an office setting. As a class, these agents are effective at reducing asthma exacerbations, improving asthma symptoms, improving respiratory function, and reducing the need for concomitant corticosteroids. Side effects for these agents were generally similar to placebo in most clinical trials.

Benralizumab

A case report from Osaka, Japan describes a 75-year-old woman who developed massive atelectasis in her the left lung resulting in tracheal deviation 4 months after initiation of benralizumab (Takimoto et al., 2020 [A]). The patient had a history of severe asthma that had previously been treated with long-acting β-agonists, leukotriene receptor antagonists, and inhaled corticosteroids for 28 years prior to her admission. After a recent hospitalization for an asthma attack, which required treatment with systemic corticosteroids and antibiotics, the patient started treatment with benralizumab to help reduce her risk of future asthma exacerbations. Four months later, the patient presented to the hospital with severe respiratory failure. The patient had markedly decreased respiratory sounds in the left lung, and a CT scan showed atelectasis by mucoid impaction. Laboratory results showed elevated blood levels of C-reactive protein level

(9.25 μg/dL) and neutrophil count (8310/μL), but with normal IgE levels and almost completely depleted blood eosinophils. The patient's sputum tested negative for both bacteria and fungi, suggesting against the presence of infection. The patient was started on systemic corticosteroids, antibiotics, and expectorants, but her respiratory status continued to worsen. The atelectasis was causing tracheal deviation leading to respiratory distress that required high-flow nasal oxygen. A bronchofiberscopy was performed to remove the thick mucus from the left main bronchus and the lower lobe bronchi, erythromycin was initiated, and benralizumab was discontinued. The patient remained in remission with no exacerbation 9 months after discontinuation of benralizumab. The investigators hypothesize that anti-IL-5 therapy may have resulted in mucus hypersecretion due to either neutrophilic inflammation or bacterial infection. In either case, treatment with a macrolide antibiotic, which have both antibacterial and neutrophil inhibitory properties, may theoretically be beneficial in treating or preventing this adverse effect of benralizumab. This is the second case of airway mucus impaction associated with benralizumab (Laviolette et al., 2013 [A]).

Dupilumab

A case study report from Okayama, Japan describes a 77-year-old Japanese man with chronic asthma who developed eosinophilic gastritis 3 months after discontinuation of dupilumab treatment (Iwamuro et al., 2020 [A]). The patient was an ex-smoker (30 cigarettes/day for 13 years) and a social drinker with history of asthma, hyperlipidemia, hypertension, atrophic rhinitis, duodenal ulcers secondary to *Helicobacter pylori* infection, hyperuricemia, prostatic hypertrophy, and overactive bladder. The patient developed an acute worsening of respiratory symptoms due to his allergic asthma, so he began treatment with dupilumab injections (dose not provided). Dupilumab is a monoclonal antibody with activity against interleukin-4 (IL-4) and interleukin-13 (IL-13). It has previously been associated with eosinophilia. In addition to the dupilumab, the patient also received inhaled fluticasone and formoterol (later switched to vilanterol), oral montelukast and azithromycin, and intravenous methylprednisolone. The dupilumab was administered only twice, with the second dose given at week 2. The dupilumab was stopped per the patient's request because his respiratory distress, cough, and sputum production were not improving. Three months later, the patient underwent a routine esophagogastroduodenoscopy for annual screening that revealed gastric ulcers in the lesser curvature of the cardia and in the posterior wall of the gastric body. These findings were deemed to be related to dupilumab discontinuation, as gastric ulcers had not been identified in previous annual check-ups. The laboratory tests showed slightly increased values for C-reactive protein (0.33 mg/dL) and Ig E (366 IU/mL), whereas white blood cells (6900 μL) and eosinophils (5.3%) were within the normal ranges. Biopsy of the gastric ulcers revealed more than 100 eosinophils per high-power field, which were infiltrating into the lamina propria and the epithelium of the gastric mucosa consistent with eosinophilic gastritis. The patient was treated with prednisone 30 mg daily, and a repeat esophagogastroduodenoscopy performed 4 weeks later showed complete resolution of gastric ulcers with no eosinophilic cells identified in the biopsy. The authors offer three hypotheses for dupilumab-associated eosinophilic gastric ulcers. First, since dupilumab stops the movement of eosinophils from blood into tissues, there may have been a pathologic redistribution of eosinophils into stomach tissue after the cessation of dupilumab. Second, while dupilumab blocks eosinophil migration into lung tissue, it may not have the same effect on gastric tissue. Third, eosinophilic gastroenteritis is frequently found in patients with atopic conditions, so this event may have been the result of the patient's underlying allergic condition rather than a drug-induced phenomenon. This is the first case of eosinophilic gastritis possibly associated with the discontinuation of dupilumab. Of note, the patient's gastric ulcers were asymptomatic. The clinical relevance of this finding remains unknown. In patients who develop unexplained gastric ulcers with eosinophilic predominance, the recent use of dupilumab should be investigated as a potentially inciting factor.

A case series describes four patients who developed unexpected eosinophilic complications after switching from anti-interleukin-5 (anti-IL-5) biologics to dupilumab for treatment of oral corticosteroid (OCS)-dependent asthma (Eger et al., 2021 [A]). The first patient was a 59-year-old woman who developed eosinophilic pneumonia after switching from benralizumab to dupilumab. Shortly after dupilumab therapy, she developed dyspnea and fever. Blood eosinophil counts had increased from 108 to 5080 cells/μL and chest CT revealed diffuse bilateral consolidations indicating eosinophilic pneumonia. Serologic tests for common parasitic infections were negative except for a few *Haemophilus influenzae* colonies. Patient's prednisone dose was increased to 60 m/day and dupilumab was discontinued. Shortly after, the patient developed acute coronary syndrome followed by cardiac arrest. She gradually recovered, the prednisone dose was tapered to 10 mg/day, and benralizumab was restarted. The second patient was a 35-year-old man who experienced asthma relapse with eosinophilia (1020 cells/μL) after switching from reslizumab to dupilumab. Prednisone 30 mg/day was restarted, but the patient's eosinophils continued to rise to nearly 5000 cells/μL. The eosinophilia did not resolve until reslizumab was restarted. The third case was a 47-year-old

woman who had been switched from reslizumab to dupilumab. Despite an initial improvement in sino-nasal symptoms, the patient developed worsening asthma symptoms and a marked increase in blood eosinophils from 90 to 1100 cells/μL. The clinical and laboratory worsening occurred as her daily oral prednisone regimen was tapered from 7.5 to 5 mg. The prednisone dose was subsequently increased, the dupilumab was discontinued, and benralizumab was initiated, and these changes resulted in an improvement in her asthma symptoms. The fourth case was 63-year-old woman who switched from benralizumab to dupilumab after a washout period of 1 year. The patient initially responded well to dupilumab, but after eight administrations of dupilumab, she suffered a minor stroke with dysarthria and left sided neurologic deficit. Lab results revealed an abrupt rise in eosinophils (3940 cell/μL) and a CT scan showed new bilateral pulmonary consolidations. The patient was suspected to have a flare of ANCA-negative eosinophilic granulomatosis with polyangiitis (EGPA). These cases highlight the importance for monitoring and screening for eosinophilic complications that may arise after discontinuation of dupilumab therapy. Importantly, the authors warn that these complications may occur even up to 1 year after discontinuing dupilumab, and the symptoms and eosinophilia may not fully resolve with oral corticosteroids alone.

Mepolizumab

A case report describes a 32-year-old woman of North African origin who developed alopecia after starting mepolizumab (Nixon et al., 2020 [A]). The patient had poorly controlled severe asthma for 2 years, with multiple hospitalizations for asthma exacerbations. She reportedly never smoked. She did have nasal polyps, for which she underwent polypectomy. Prior to starting mepolizumab, her medication regimen included oral prednisolone 20 mg per day, inhaled fluticasone 250 μg/formorterol 10 μg 2 puffs twice daily metered dose inhaler via spacer, inhaled tiotropium, and omeprazole for gastroesophageal reflux disease. After her first dose of mepolizumab, the patient experienced headaches, myalgia, and occasional urticaria, none of which were severe enough to warrant discontinuation of treatment. After 4 months of mepolizumab therapy, she reported no improvement in symptoms, one asthma exacerbation, and, interestingly, hair loss from her head. She continued on mepolizumab for an additional 2 months before treatment was discontinued due to worsening of her asthma. Dermatology reviewed her scalp, noted that there was no evidence of scarring, and did not identify a cause for her alopecia. The patient later started treatment with reslizumab, and she experienced improvement in hair loss and asthma symptoms.

However, she ultimately ended up discontinuing therapy due to a constant severe sore throat. The author's attributed this patient's reversible hair loss to the mepolizumab. While the authors describe this as the first published case of mepolizumab-induced hair loss, they also not that they have since observed this phenomenon in two additional cases. Of note, they describe that all three of these cases occurred in women of North African origin, all had worsening symptoms of urticaria upon treatment with mepolizumab, and all had improvement in asthma symptoms and alopecia after switching from mepolizumab to either reslizumab or benralizumab. The authors suggest that mepolizumab-associated alopecia may be related to an immune-complex reaction, and they further hypothesize that the presence of alopecia may be an early warning sign of therapeutic failure with mepolizumab for the treatment of severe asthma.

Omalizumab

A meta-analysis evaluated 3 studies with 4 publications comparing omalizumab versus placebo for treatment of moderate to severe asthma in 1380 children and adolescents ranging from 6 to 20 years of age (Fu et al., 2020 [M]). The meta-analysis did not find any new adverse events associated with omalizumab. However, it did find a statistically significant lower rate of severe adverse events in the omalizumab group versus the placebo group (30/85 vs 451/526, respectively, Odds Ratio 0.36; 95% Confidence interval 0.22–0.57, P value <0.001). These finding add support for the safety of using omalizumab in pediatric and adolescent patients with moderate to severe asthma.

Reslizumab

A recent review article evaluated the adverse events associated with long-term intravenous reslizumab (3.0 mg/kg) use (Virchow et al., 2020 [M]). Five placebo-controlled and 1 open-label extension trial including patients 12 to 75 years of age with moderate to severe or eosinophilia asthma were used to evaluate the use of reslizumab ($n = 1028$) over a minimum of 15 weeks. The authors found that there were more patients with at least 1 adverse event in the placebo group ($n = 730$) than in the reslizumab group, (81% vs 67%, respectively, RR 0.83, 95% confidence interval 0.79–0.89). Similarly, there were more patients with at least 1 serious adverse event in the placebo group than the reslizumab group (9% vs 6%, respectively, 95% confidence interval 0.5–0.97). The only adverse event reported with reslizumab that had more than a 1% increase compared to placebo was anaphylaxis. The 6 patients ($n < 1\%$) who experienced anaphylaxis were successfully treated with standardized treatment.

Patients on reslizumab were more likely to report vascular disorder side effects, ear and labyrinth disorders, urinary tract infections and oropharyngeal pain compared to placebo, but these events were statistically significantly different from the placebo group (95% confidence interval of 0.68–2.09, 0.48–2.21, 0.60–1.69 and 0.65–2.21, respectively). The authors note that this pooled analysis provides evidence that reslizumab is safe to use beyond 1 year in patients with moderate to severe asthma associated with eosinophilia.

References

Acharya, N., Sharma, S. K., et al. (2020). Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial. *Rheumatology International*, 40(5), 703–710. https://doi.org/10.1007/s00296-020-04565-w [c].

Ameri, P., Giacomo, T., et al. (2021). Cardiovascular safety of the tyrosine kinase inhibitor nintedanib. *British Journal of Clinical Pharmacology*, 2021, 1–9. https://doi.org/10.1111/bcp.14793 [R].

Amini, A., Koury, E., et al. (2020). Nintedanib-induced colitis treated effectively with budesonide. *Cureus*, 12(7), e9489. https://doi.org/10.7759/cureus.9489 [A].

Antoniou, K., Markopoulou, K., et al. (2020). Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: A retrospective, observational, cohort study. *ERJ Open Research*, 6(1), 00172–02019. https://doi.org/10.1183/23120541.00172-2019 [C].

Arunprasath, P., Rai, R., et al. (2020). Pirfenidone-induced dose-dependent phototoxicity—A distinct drug reaction. *Indian Dermatology Online Journal*, 11(6), 1007–1009. https://doi.org/10.4103/idoj.IDOJ_40_20 [A].

Azuma, A., Chung, L., et al. (2021). Efficacy and safety of nintedanib in Asian patients with systemic sclerosis-associated interstitial lung disease: Subgroup analysis of the SENSCIS trial. *Respiratory Investigation*, 59(2), 252–259. https://doi.org/10.1016/j.resinv.2020.10.005 [C].

Banerjee, M., Haj Ahmed, E., et al. (2020). Unilateral mydriasis in a child with a ventriculoperitoneal shunt for obstructive hydrocephalus: A diagnostic dilemma. *BML Case Reports*, 13(12), e237257. https://doi.org/10.1136/bcr-2020-237257 [A].

Bournia, V. K., Distler, O., et al. (2021). Diarrhoea in systemic sclerosis patients as a nocebo effect of nintedanib. *The European Respiratory Journal*, 57(4), 2003021. https://doi.org/10.1183/13993003.03021-2020 [R].

Cameli, P., Refini, R. M., et al. (2020). Long-term follow-up of patients with idiopathic pulmonary fibrosis treated with pirfenidone or nintedanib: A real-life comparison study. *Frontiers in Molecular Biosciences*, 7, 581828. https://doi.org/10.3389/fmolb.2020.581828 [C].

Chandler, R. E. (2020). Nintedanib and ischemic colitis: Signal assessment with the integrated use of two types of real-world evidence, spontaneous reports of suspected adverse drug reactions, and observational data from large health-care databases. *Pharmacoepidemiology and Drug Safety*, 29(8), 951–957. https://doi.org/10.1002/pds.5022 [R].

Chung, M. P., Park, M. S., et al. (2020). Safety and efficacy of pirfenidone in advanced idiopathic pulmonary fibrosis: A nationwide post-marketing surveillance study in Korean patients. *Advances in Therapy*, 37(5), 2303–2316. https://doi.org/10.1007/s12325-020-01328-8 [C].

Corral, M., DeYoung, K., et al. (2020). Treatment patterns, healthcare resource utilization, and costs among patients with idiopathic pulmonary fibrosis treated with antifibrotic medications in US-based commercial and Medicare supplemental claims databases: A retrospective cohort study. *BMC Pulmonary Medicine*, 20(1), 188. https://doi.org/10.1186/s12890-020-01224-5 [C].

Dhooria, S., Agarwal, R., et al. (2020). A real-world study of the dosing and tolerability of pirfenidone and its effect on survival in idiopathic pulmonary fibrosis. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases*, 37(2), 148–157. https://doi.org/10.36141/svdld.v7i2.8718 [C].

Di Salvo, E., Patella, V., et al. (2020). The leukotriene receptor antagonist montelukast can induce adverse skin reactions in asthmatic patients. *Pulmonary Pharmacology & Therapeutics*, 60, 101875. https://doi.org/10.1016/j.pupt.2019.101875 [A].

Dull, S. K., Jagan, N., et al. (2020). Diffuse alveolar hemorrhage following pirfenidone initiation. *Journal of Pharmacy Practice*, 33(4), 548–552. https://doi.org/10.1177/0897190019841731 [A].

Eaden, J. A., Barber, C. M., et al. (2020). Real world experience of response to pirfenidone in patients with idiopathic pulmonary fibrosis: A two Centre retrospective study. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases*, 37(2), 218–224. https://doi.org/10.36141/svdld.v37i2.8587 [C].

Eger, K., Pet, L., et al. (2021). Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma. *The Journal of Allergy and Clinical Immunology. In Practice*, 9(7), 2913–2915. https://doi.org/10.1016/j.jaip.2021.02.042 [A].

Fu, Z., Xu, Y., et al. (2020). Efficacy and safety of omalizumab in children with moderate-to-severe asthma: A meta-analysis. *The Journal of Asthma*, 58(10), 1350–1358. https://doi.org/10.1080/02770903.2020.1789875 [M].

Harari, S., Specchia, C., et al. (2020). Older idiopathic pulmonary fibrosis male patients are at a higher risk of nintedanib dose reduction. *Respiration*, 99(8), 646–648. https://doi.org/10.1159/000508667 [c].

Hasegawa, M., Uehara, A., et al. (2020). Nintedanib-induced glomerular microangiopathy: A case report. *CEN Case Reports*, 9(4), 295–300. https://doi.org/10.1007/s13730-020-00474-w [A].

Highland, K. B., Distler, O., et al. (2021). Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: A subgroup analysis of the SENSCIS trial. *The Lancet Respiratory Medicine*, 9(1), 96–106. https://doi.org/10.1016/S2213-2600(20)30330-1 [C].

Hirasawa, Y., Abe, M., et al. (2020). Tolerability of nintedanib-related diarrhea in patients with idiopathic pulmonary fibrosis. *Pulmonary Pharmacology & Therapeutics*, 62, 101917. https://doi.org/10.1016/j.pupt.2020.101917 [c].

Imai, R., & Tomishima, Y. (2020). Left ventricular dysfunction in an idiopathic pulmonary fibrosis patient on nintedanib. *Respirology Case Reports*, 8(2), e00533. https://doi.org/10.1002/rcr2.533 [A].

Iwamuro, M., Murakami, T., et al. (2020). Eosinophilic gastritis in a patient previously treated with dupilumab. *Case Reports in Gastrointestinal Medicine*, 2020, 6381670. https://doi.org/10.1155/2020/6381670 [A].

Jiménez, M. L., Carrasco, C. H., et al. (2020). Severe hepatotoxicity secondary to nintedanib. *Revista Española de Enfermedades Digestivas*. https://doi.org/10.17235/reed.2020.7585/2020 [A].

Justet, A., Klay, D., et al. (2021). Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation. *The European Respiratory Journal*, 57, 2003198. https://doi.org/10.1183/13993003.03198-2020 [c].

Kanayama, M., Mori, M., et al. (2020). Perioperative pirfenidone treatment for lung cancer patients with idiopathic pulmonary fibrosis. *Surgery Today*, 50(5), 469–474. https://doi.org/10.1007/s00595-019-01923-5 [c].

Kuwana, M., Ogura, T., et al. (2021). Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. *Modern Rheumatology*, 31(1), 141–150. https://doi.org/10.1080/14397595.2020.1751402 [c].

Lasky, J. A., Criner, G. J., et al. (2020). Safety of nintedanib in patients with idiopathic pulmonary fibrosis: Global pharmacovigilance data. *Advances in Therapy*, 37(10), 4209–4219. https://doi.org/10.1007/s12325-020-01452-5 [C].

Laviolette, M., Gossage, D. L., et al. (2013). Effects of benralizumab on airway eosinophils in asthma with sputum eosinophilia. *The Journal of Allergy and Clinical Immunology*, 132(5), 1086–1096. https://doi.org/10.1016/j.jaci.2013.05.020 [A].

Lee, L. A., Bailes, Z., et al. (2021). Efficacy and safety of once-daily single-inhaler triple therapy (Ff/umec/vi) versus FF/VI in patients with inadequately controlled asthma (Captain): A double-blind, randomised, phase 3A trial. *The Lancet Respiratory Medicine*, 9(1), 69–84. https://doi.org/10.1016/S2213-2600(20)30389-1 [C].

Lee, H. W., Park, J., et al. (2020). Comparisons of exacerbations and mortality among LAMA/LABA combinations in stable chronic obstructive pulmonary disease: Systematic review and Bayesian network meta-analysis. *Respiratory Research*, 21(1), 310. https://doi.org/10.1186/s12931-020-01540-8 [M].

Liang, J., Cao, H., et al. (2021). Efficacy and tolerability of nintedanib in idiopathic-inflammatory-myopathy-related interstitial lung disease: A pilot study. *Frontiers in Medicine*, 8, 626953. https://doi.org/10.3389/fmed.2021.626953 [c].

Madgula, A. S., Covello, B. R., et al. (2020). Talaromycosis in a patient on nintedanib for interstitial lung disease. *Cureus*, 12(3), e7215. https://doi.org/10.7759/cureus.7215 [A].

Maher, T. M., Corte, T. J., et al. (2020). Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: A double-blind, randomised, placebo-controlled, phase 2 trial. *The Lancet Respiratory Medicine*, 8(2), 147–157. https://doi.org/10.1016/S2213-2600(19)30341-8 [C].

Majewski, S., Białas, A. J., et al. (2020). A multicentre retrospective observational study on polish experience of pirfenidone therapy in patients with idiopathic pulmonary fibrosis: The PolExPIR study. *BMC Pulmonary Medicine*, 20(1), 122. https://doi.org/10.1186/s12890-020-1162-6 [C].

Moor, C. C., Mostard, R. L. M., et al. (2020). Patient expectations, experiences and satisfaction with nintedanib and pirfenidone in idiopathic pulmonary fibrosis: A quantitative study. *Respiratory Research*, 21(1), 196. https://doi.org/10.1186/s12931-020-01458-1 [c].

Narváez, J., Vicens-Zygmunt, V., et al. (2020). Nintedanib for the treatment of refractory progressive rheumatoid arthritis-related interstitial lung disease: A real-life case series. *Rheumatology*, 59(12), 3983–3986. https://doi.org/10.1093/rheumatology/keaa503 [A].

Nixon, R., Despiney, R., et al. (2020). Case of paradoxical adverse response to mepolizumab with mepolizumab-induced alopecia in severe eosinophilic asthma. *BML Case Reports*, 13(2), e233161. https://doi.org/10.1136/bcr-2019-233161 [A].

Ogata, H., Nakagawa, T., et al. (2021). Nintedanib treatment for pulmonary fibrosis after coronavirus disease 2019. *Respirology Case Reports*, 9(5), e00744. https://doi.org/10.1002/rcr2.744 [A].

Richeldi, L., Kolb, M., et al. (2020). Efficacy and safety of nintedanib in patients with advanced idiopathic pulmonary fibrosis. *BMC Pulmonary Medicine*, 20(1), 3. https://doi.org/10.1186/s12890-019-1030-4 [C].

Seibold, J. R., Maher, T. M., et al. (2020). Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: Data from the SENSCIS trial. *Annals of the Rheumatic Diseases*, 79(11), 1478–1484. https://doi.org/10.1136/annrheumdis-2020-217331 [C].

Senoo, S., Miyahara, N., et al. (2020). Nintedanib can be used safely and effectively for idiopathic pulmonary fibrosis with predicted forced vital capacity ≤ 50%: A multi-center retrospective analysis. *PLoS One*, 15(8), e0236935. https://doi.org/10.1371/journal.pone.0236935 [c].

Sentinel Initiative. (2019). *Neuropsychiatric events following montelukast use: A propensity scare matched analysis*. https://www.sentinelinitiative.org/drugs/assessments/neuropsychiatric-events-following-montelukast-use-propensity-score-matched [C].

Shiratori, T., Tanaka, H., et al. (2020). Effect of nintedanib on non-small cell lung cancer in a patient with idiopathic pulmonary fibrosis: A case report and literature review. *Thoracic Cancer*, 11(6), 1720–1723. https://doi.org/10.1111/1759-7714.13437 [A].

Song, J. W., Ogura, T., et al. (2020). Long-term treatment with nintedanib in Asian patients with idiopathic pulmonary fibrosis: Results from INPULSIS®-ON. *Respirology*, 25(4), 410–416. https://doi.org/10.1111/resp.13647 [C].

Sunther, M., Marchon, K., et al. (2021). Tiotropium in the management of paediatric and adolescent asthma: Systematic review. *Paediatric Respiratory Reviews*, 38, 58–62. https://doi.org/10.1016/j.prrv.2020.08.003 [M].

Takeda, T., Kunimatsu, Y., et al. (2020). Improvement in subjective symptoms and tolerability in response to nintedanib treatment in elderly patients with idiopathic pulmonary fibrosis. *Journal of Clinical Medicine*, 9(3), 755. https://doi.org/10.3390/jcm9030755 [c].

Takimoto, T., Kagawa, T., et al. (2020). Massive atelectasis by mucoid impaction in an asthma patient during treatment with anti-interleukin-5 receptor antibody. *Respirology Case Reports*, 8(66), e00599. https://doi.org/10.1002/rcr2.599 [A].

Tang, W., Yu, T., et al. (2020). Nintedanib in bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation. *Chest*, 158(3), e89–e91. https://doi.org/10.1016/j.chest.2020.05.557 [A].

Uchida, Y., Ikeda, S., et al. (2021). Tolerability and safety of nintedanib in elderly patients with idiopathic pulmonary fibrosis. *Respiratory Investigation*, 59(1), 99–105. https://doi.org/10.1016/j.resinv.2020.08.003 [c].

US Food and Drug Administration. (2020). *FDA requires Boxed Warning about serious mental health effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug.

Vacchi, C., Manfredi, A., et al. (2020). Combination therapy with nintedanib and sarilumab for the management of rheumatoid arthritis related interstitial lung disease. *Case Reports in Medicine*, 2020, 6390749. https://doi.org/10.1155/2020/6390749 [A].

Vianello, A., Salton, F., et al. (2020). Nintedanib treatment for idiopathic pulmonary fibrosis patients who have been switched from pirfenidone therapy: A retrospective case series study. *Journal of Clinical Medicine*, 9(2), 422. https://doi.org/10.3390/jcm9020422 [c].

Virchow, J. C., Katial, R., et al. (2020). Safety of reslizumab in uncontrolled asthma with eosinophilia: A pooled analysis from 6 trials. *The Journal of Allergy and Clinical Immunology. In Practice*, 8(2), 540–548.e1. https://doi.org/10.1016/j.jaip.2019.07.038 [M].

Wells, A. U., Flaherty, K. R., et al. (2020). Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: A randomised, double-blind, placebo-controlled, parallel-group trial. *The Lancet Respiratory Medicine*, 8(5), 453–460. https://doi.org/10.1016/S2213-2600(20)30036-9 [C].

Yang, D., Peng, Q., et al. (2020). Can tiotropium add-on therapy safely improve clinical outcomes in children and adolescents with persistent asthma? *Annals of Allergy, Asthma & Immunology*, 125(1), 109–110. https://doi.org/10.1016/j.anai.2020.04.022 [M].

Yang, M., Zhang, Y., et al. (2020). Association of tiotropium use and the risk of adverse cardiovascular events in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized controlled trials. *European Journal of Clinical Pharmacology*, 76(6), 795–805. https://doi.org/10.1007/s00228-020-02853-9 [M].